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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/715,417	STRATEN ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,12,13 and 17-50* is/are pending in the application.

4a) Of the above claim(s) *12,13,18,19,29-31 and 41-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,17,20-28,32-40 and 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/24/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 9/24/07 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election with traverse of Group I (claims 1-40), and species of SEQ ID NO: 14 as the native human survivin peptide sequence and SEQ ID NO: 36 as the modified survivin peptide in Applicant's response filed 12/21/06.

The declaration under 37 CFR 1.132 of Dr. Mads Hald Andersen filed 9/24/07 is acknowledged and has been entered.

Claims 1, 17, 20-28, 32-40 and 50 are currently being examined.

The following are new grounds of rejection necessitated by Applicant's amendment filed 9/24/07.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 17, 20-28, 32-40 and 50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed invention, (1) the MHC class I restricted epitope peptides recited in the instant claims that are or comprise SEQ ID NO: 1, 4 and/or 14, and composition thereof or pharmaceutical composition thereof, vaccine thereof , HLA class I/peptide complex or multimer complex thereof, and kit thereof, and (2) a composition or pharmaceutical composition or vaccine composition comprising an MHC class I restricted epitope peptide comprising or consisting of SEQ ID NO: 5 and/or 36, (3) an MHC class I restricted epitope peptide *comprising* SEQ ID NO: 5 or 36.

The instant claims encompass the claims encompass an MHC class I-restricted epitope peptide, pharmaceutical composition, vaccine and kit: (1) an MHC class I restricted epitope peptide *derived* from survivin *comprising* an epitope peptide that is one of SEQ ID NO: 1, 4, 5 or 14 with undisclosed N- and C-terminal flanking sequences, (2) an MHC class I restricted peptide that is capable of binding to an HLA class I molecule, but isn't capable of *in situ* detection in a tumor tissue of CTLs that are reactive with the epitope peptide, (3) a peptide that is capable of eliciting INF-γ producing cells in a PBL population of a cancer patient at a frequency of at least 10 per 10^4 recited in instant claim 21, (4) a peptide that is capable of eliciting INF-γ producing cells in a PBL population of a cancer patient wherein CTL produced have cytotoxic effects against survivin expressing cells of a cancer cell line, including the two recited in instant claim 24, (5) a pharmaceutical composition comprising said peptide, including a composition comprising said peptide having a subsequence of a native survivin and another that is a modified subsequence, and including wherein the peptides are SEQ ID NO: 36 and 14, (6) a vaccine composition comprising the said peptide, including wherein it is capable of eliciting an immune response against a cancer disease including wherein survivin is expressed, a multiepitope vaccine thereof, and including wherein the vaccine elicits the production *in vivo* of effector T cells having a cytotoxic effect against cancer cells, (7) the claimed kit comprising the peptide, and (8) the complex comprising the peptide. There is insufficient disclosure in the specification on such peptides, composition, vaccine, kit and complex thereof.

There is insufficient disclosure in the specification on such peptides, composition, vaccine, kit and complex thereof.

The specification discloses that "survivin is a recently identified member of the family of inhibitors of apoptosis proteins (IAPs)" ([0009]), and that "U.S. Pat. No. 6,245,523 discloses the isolation of purified survivin and it provides nucleic acid molecules that encode the survivin protein, and antibodies and other molecules that bind to survivin U.S. Pat. No. 6,245,523 also discloses anti-apoptotically active fragments of the survivin protein and variants hereof wherein an amino acid residue has been inserted N- or C-terminal to, or within, the disclosed survivin sequence. It is specifically disclosed that such peptides should contain key functional residues required for apoptosis, *i.e.,* Trp at position 67, Pro at position 73 and Cys at position 84" ([0011]). The specification discloses that "survivin is a recently identified member of the family of inhibitors of apoptosis proteins (IAPs). In a global gene expression analysis of about 4 million transcripts, survivin was identified as one of the top genes invariably up-regulated in many types of cancer but not in normal tissue (8)" [0009].

The specification further discloses that the peptides of the invention are derived from the known sequence of survivin, *e.g.,* the sequence disclosed in U.S. Pat. No. 6,245,523, and that the selection of peptides potentially having the ability to bind to a particular HLA molecule can be made by the alignment of known sequences that bind to a given particular HLA molecule to thereby reveal the predominance of a few related amino acids at particular positions in the peptides, *i.e.,* anchor residues ([0027]). The specification discloses "a simple approach to identifying peptides of the invention includes the following steps: selecting a particular HLA molecule, e.g. one occurring at a high rate in a given population, carrying out an alignment analysis as described above to identify "anchor residue motifs" in the survivin protein, isolating or constructing peptides of a suitable size that comprise one or more of the identified anchor residues and testing the resulting peptides for (i) capability to bind to the particular HLA molecule using the assembly assay as described herein, (ii) the capability of the peptides to elicit INF-.gamma.-producing cells in a PBL population of a cancer patient at a frequency of at least 1 per 10.sup.4 PBLs as determined by an ELISPOT assay as described herein, and/or (iii) the capability of the peptides to detect *in situ* in a tumour tissue CTLs that are reactive with the epitope peptides being tested" ([0031]).

Celis *et al* (Mol. Immunol. 1994. 31(18): 1423-1430, of record) teach that in order to establish whether a peptide is immunogenic said peptide needs to be tested in assays that actually establish that a peptide is immunogenic. Celis *et al* teach that "In addition to MHC binding, other factors such as antigen processing, peptide transport and the composition of the T-cell receptor repertoire could determine whether any of these peptides can function as effective CTL antigens. Ochoa-Garay *et al* (Mol. Immunol. 1997. 34(1): 273-281, of record) teach that "In summary, the results in this report indicate that the immunogenicity of a peptide cannot always be predicted from its affinity for class I or the presence of class I binding motifs. In addition, our data show that variables such as CTL precursor frequency, peptide hydrophobicity and stability can influence the *in vitro* induction of CTL responses" (especially page 279, last sentence and continuing onto page 280). Karin *et al* (of record) teach that a single substitution in an amino acid, wherein said amino acid plays no role in MHC binding can completely abrogate the immunogenicity of an otherwise immunogenic peptide (especially Summary and Table 1).

In addition, the art recognizes that for a peptide to be a T cell epitope, the length of the peptide is important for binding to HLA (along with the presence of anchor (or "motif") amino acid residues present within the peptide). The peptides that bind to class I molecules have a predominant length, *i.e.,* a minimum of 8 or 9 amino acid residues for a class I MHC restricted T cell epitope peptide. A primary factor for this is that amino acid residues at the amino- and carboxy-termini of peptides binding to class I molecules interact with conserved amino acid residues in pockets ("A","F") located at opposite ends of the binding groove

of the class I molecule, giving rise to a common orientation of the peptides in the binding site (Engelhard at page 14, column 1, lines 16-27, Curr. Opin. Biol. 1994, 6: 13-23, of record) Thus, the amino acid residues at the peptides' termini make a network of hydrogen bonds with conserved residues on the sides and bottom of the peptide binding groove of class I molecules. These interactions are important for holding the peptides in the binding groove and for stabilizing the complex (Guo *et al* at page 366, column 1 lines 1-10, Nature 1992, 360: 364-366, of record) "...the preferred length (of the peptide) is determined by the minimum amount of peptide required to span the center of the binding site and optimize the interactions at the ends", but that the predominant length is 9 amino acid residues (Engelhard at page 14, column 1, lines 23-27, of record).

The specification discloses that some nonamer and decamer peptides that are subsequences of human survivin or substitution variants of said peptides can bind to selected HLA class I molecules (especially Table 4). The specification discloses that five stage IV melanoma patients were vaccinated with the modified HLA-A2 restricted sur1M2 peptide (SEQ ID NO: 5) loaded onto autologous dendritic cells, resulting in a strong T cell response to said peptide, and the detection of infiltration of survivin reactive cells into visceral and soft tissue metastases using *in situ* peptide/HLA-A2 multimer staining (page 44 at lines 4-11). The specification discloses that SEQ ID NO; 1, 4 and 5 bind to HLA-A2 with *C50* of 30, 1 and 1 uM, respectively, and that CTL or TIL from some CLL or melanoma patients could recognize or cross-react with complexes of SEQ ID NO: 5 and HLA-A2 (especially Table 1). The specification discloses injection of dendritic cell loaded SEQ ID NO: 5, 10 or 3 into cancer patients, and demonstration of induction of HLA-A2/SEQ ID NO: 10-specific T cells with the capacity to home to soft tissue and visceral metastases (especially pages 44-48), but does not disclose the relevance of the treatment with the clinical outcome observed, *i.e.,* how the composition or vaccine comprising the peptides treat or prevent cancer.

Evidentiary reference Matthias *et al* (Blood. 2005, 106(11), part 2, pp 369B, abstract 3, 5145, of record) teach that a survivin peptide specific CTL could be detected in individuals with multiple myeloma, and those same CTL were detected in 5% of healthy individuals.

Evidentiary reference Celis (J. Clin. Invest. 2002, 110(12: 1765-1768, of record) teaches that "Unfortunately, the advantages that peptide vaccines have to offer are to some extent diminished by their inherent lack of immunogenicity, which so far has been reflected by their not-so-spectacular results in the clinic. Because the immune system in most species has evolved through time to fight life threatening infectious agents (and perhaps tumors), it should not be surprising that vaccines consisting of aseptic, endotoxin-free peptides are likely to be ignored and will likely be ineffective at inducing T cell immunity. In addition, peptides that are injected in aqueous solutions will be unsuccessful at stimulating

CTL responses, either because of their rapid biodegradation (*e.g.*, by proteases) or, worse, because of the induction of T cell tolerance/anergy, which results from the antigenic stimulation of CTLs by non-professional APCs." Celis further teaches that an additional complication resulting from the use of synthetic peptide-derived vaccines is the induction of low affinity CTLs, that while capable of killing target cells that are exogenously pulsed with peptide, are not able to recognize the target cells that naturally process and present the peptide epitope, such as malignant cells. These low quality CTLs would have little effect in fighting and controlling disease (especially page 1765 through the paragraph spanning pages 1765-1766.

Evidentiary reference Marchand *et al* (Exp. Opin. Biol. Therapy. 1(3): 497-510, 2001, of record) teach "It is fair to say that in patients vaccinated with defined antigen, the immune responses induced have been so far very poor, if present. In some studies, immune responses were reported for some patients but without any correlation with the clinical responses. In addition, some patients with complete and long-term regressions of several melanoma metastases failed to mount a detectable response against the antigen present in the vaccine." (last paragraph at column 2 on page 505).

Evidentiary reference Morel *et al* (Immunity 12: 107-117, 2000, of record) teach the treatment of target cells for at least one week with IFN-γ to induce immunoproteasome expression in said target cells, and further teach that a number of antigenic peptides that are efficiently produced by the standard proteasome are not produced by the immunoproteasome. Morel *et al* further teach that a major difference between the two forms of proteasomes in terms of catalytic activity is the severely reduced ability of the immunoproteasome to cleave after acidic residues and also after residues with branched side chains, such as valine (paragraph spanning pages 113-114). Morel *et al* teach that an IFN-γ rich environment such as that found in a lymph node or a tumor mass heavily infiltrated with T cells could cause a proteasome switch in the tumor cells resulting in a lack of presentation of certain tumor antigens and escape from CTL attack (especially first sentence of the third full paragraph at column 1 on page 114).

Evidentiary reference Andersen *et al* (Cancer Res. 2000, 61: 869-872, IDS reference) teach that they have demonstrated the existence of T cell responses against two survivin deduced epitopes in cancer patients, and "However, at this time we do not know whether *survivin* peptides are actually presented by the tumor cells *in vivo*, because the formal proof for this notion is still lacking" (last paragraph of article).

Evidentiary reference Andersen *et al* (Cancer Res. 2001, 61: 5964-5968, IDS reference) teach that "The ELISPOT methodology represents a strong tool to monitor peptide-specific T-cell response. However, although it has been shown that ELISPOT reactivity in most cases correlates with the capacity to lyse the target cell, the formal proof for this notion can be given only directly" (page 5966 at column 2, lines 3-7).

The specification discloses that SEQ ID NO: 36 recited in the pharmaceutical composition of instant claim 27 does bind HLA-A1 with a *C50* of 1 uM, but does not disclose if the peptide is immunogenic, and does not disclose that the second peptide in the said pharmaceutical composition SEQ ID NO: 14 binds any HLA class I molecule or is immunogenic (especially Table 4). The disclosed use of a pharmaceutical composition of the invention is to treat cancer ([0022]).

Evidentiary reference Andersen *et al* (Cancer Res. 2000, 61: 869-872, IDS reference) teach that the peptide STFKNWPFL (that is SEQ ID NO: 14 of instant claim 27) does not bind HLA-A2 (especially Table 1), thus indicating that the said peptide would not be useful in a pharmaceutical composition to treat an HLA-A2 positive patient.

Evidentiary reference Reker *et al* (Cancer Biol. & Therapy. 2004, 3(2): 173-179, of record) teach "To date, it is not known whether survivin is indeed a tumor rejection antigen, *i.e.,* a tumor-associated antigen that can elicit immune responses in patients, which significantly impacts tumor growth...Thus if efficient immunity can be successfully elicited in cancer patients, without the induction of severe autoimmunity, survivin clearly becomes a prime candidate for a widely applicable cancer vaccine" (last paragraph of article).

The specification does not disclose any peptide or composition thereof used prophylactically as a vaccine.

Evidentiary reference the Merck Manual (of record) teaches that a vaccine is a suspension of whole or fractionated bacteria or viruses that have been rendered nonpathogenic and is given to induce an immune response and prevent subsequent disease.

Evidentiary reference Encyclopedia Brittanica Online (of record) defines vaccine as a suspension of weakened, killed, or fragmented microorganisms or toxins or of antibodies or lymphocytes that is administered primarily to prevent disease.

The art recognizes that in order to be used for generating an immunogenic response, *i.e.,* for it to be an epitope, and also hence by extension to be used for *ex vivo* or *in situ* diagnosis of survivin reactive T cells of a cancer patient, that the said peptide must bind MHC and also present an epitope recognized by T cells.

There is no disclosure in the specification that the peptides consisting of or comprising SEQ ID NO: 1, 4, 14 and 36 constitute a T cell epitope.

Even if there were factual evidence that patients with melanoma or any other cancer or pathological condition could produce a peptide-specific immune response to the claimed peptide in a pharmaceutical composition, there is no factual evidence that the patient's condition would clinically improve, *i.e.,* be 'treated', nor that a vaccine comprising the peptide could prevent a cancer. Based upon the teachings of the evidentiary references cited herein, it is evident that eliciting an immune response is not sufficient to evoke a clinically significant or specific anti-tumor effect. The specification does not disclose the identity of the amino acid residues that flank the recited SEQ ID NO that would allow the peptide comprising the recited SEQ ID NO to bind to an HLA class I molecule or be processed to one that could bind.

Adequate written description requires more than a mere statement that it is part of the invention.

Given these considerations, adequate written description has not been established.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in the amendment filed 9/24/07 on page 24, briefly that Applicant's remarks concerning the enablement rejection (enunciated below) apply herein.

It is the Examiner's position that the instant rejection stands for the reasons of record, and as enunciated herein. The Examiner's position regarding Applicant's arguments to the enablement rejection may be found below.

5. Claims 1, 17, 20-28, 32-40 and 50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO: 5, kit thereof, HLA-A2/complex or multimer complex thereof, does not reasonably provide enablement for (1) the MHC class I restricted epitope peptides recited in the instant claims that are or comprise SEQ ID NO: 1, 4 and/or 14, and composition thereof or pharmaceutical composition thereof, vaccine thereof , HLA class I/peptide complex or multimer complex thereof, and kit thereof, and (2) a composition or pharmaceutical composition or vaccine composition comprising an MHC class I restricted epitope peptide comprising or consisting of SEQ ID NO: 5 and/or 36, (3) an MHC class I restricted epitope peptide *comprising* SEQ ID NO: 5 or 36. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification has not enabled the breadth of the claimed invention because the claims encompass an MHC class I-restricted epitope peptide, pharmaceutical composition, vaccine and kit: (1) an MHC class I restricted epitope peptide *derived* from survivin *comprising* an epitope peptide that is one of SEQ ID NO: 1, 4, 5 or 14 with undisclosed N- and C-terminal flanking sequences, (2) an MHC class I restricted peptide that is capable of binding to an HLA class I molecule, but isn't capable of *in situ* detection in a tumor tissue of CTLs that are reactive with the epitope peptide, (3) a peptide that is capable of eliciting INF-γ producing cells in a PBL population of a cancer patient at a frequency of at least 10 per 10^4 recited in instant claim 21, (4) a peptide that is capable of eliciting INF-γ producing cells in a PBL population of a cancer patient wherein CTL produced have cytotoxic effects against survivin expressing cells of a cancer cell line, including the two recited in instant claim 24, (5) a pharmaceutical composition comprising said peptide, including a composition comprising said peptide having a subsequence of a native survivin and another that is a modified subsequence, and including wherein the peptides are SEQ ID NO: 36 and 14, (6) a vaccine composition comprising the said peptide, including wherein it is capable of eliciting an immune response against a cancer disease including wherein survivin is expressed, a multiepitope vaccine thereof, and including wherein the vaccine elicits the production *in vivo* of effector T cells having a cytotoxic effect against cancer cells, (7) the claimed kit comprising the peptide, and (8) the complex comprising the peptide. There is insufficient disclosure in the specification on such peptides, composition, vaccine, kit and complex thereof.

The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed invention can be made and/or used.

The specification discloses that "survivin is a recently identified member of the family of inhibitors of apoptosis proteins (IAPs)" ([0009]), and that "U.S. Pat. No. 6,245,523 discloses the isolation of purified survivin and it provides nucleic acid molecules that encode the survivin protein, and antibodies and other molecules that bind to survivin U.S. Pat. No. 6,245,523 also discloses anti-apoptotically active fragments of the survivin protein and variants hereof wherein an amino acid residue has been inserted N- or C-terminal to, or within, the disclosed survivin sequence. It is specifically disclosed that such peptides should contain key functional residues required for apoptosis, *i.e.,* Trp at position 67, Pro at position 73 and Cys at position 84" ([0011]). The specification discloses that "survivin is a recently identified member of the family of inhibitors of apoptosis proteins (IAPs). In a global gene expression analysis of about 4 million transcripts, survivin was identified as one of the top genes invariably up-regulated in many types of cancer but not in normal tissue (8)" [0009].

The specification further discloses that the peptides of the invention are derived from the known sequence of survivin, *e.g.,* the sequence disclosed in U.S. Pat. No. 6,245,523, and that the selection of peptides potentially having the ability to bind to a particular HLA molecule can be made by the alignment of known sequences that bind to a given particular HLA molecule to thereby reveal the predominance of a few related amino acids at particular positions in the peptides, *i.e.,* anchor residues ([0027]). The specification discloses "a simple approach to identifying peptides of the invention includes the following steps: selecting a particular HLA molecule, e.g. one occurring at a high rate in a given population, carrying out an alignment analysis as described above to identify "anchor residue motifs" in the survivin protein, isolating or constructing peptides of a suitable size that comprise one or more of the identified anchor residues and testing the resulting peptides for (i) capability to bind to the particular HLA molecule using the assembly assay as described herein, (ii) the capability of the peptides to elicit INF-.gamma.-producing cells in a PBL population of a cancer patient at a frequency of at least 1 per 10.sup.4 PBLs as determined by an ELISPOT assay as described herein, and/or (iii) the capability of the peptides to detect *in situ* in a tumour tissue CTLs that are reactive with the epitope peptides being tested" ([0031]).

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In addition, the art recognizes that for a peptide to be a T cell epitope, the length of the peptide is important for binding to HLA (along with the presence of anchor (or "motif") amino acid residues present within the peptide). The peptides that bind to class I molecules have a predominant length, *i.e.,* a minimum of 8 or 9 amino acid residues for a class I MHC restricted T cell epitope peptide. A primary factor for this is that amino acid residues at the amino- and carboxy-termini of peptides binding to class I molecules interact with conserved amino acid residues in pockets ("A","F") located at opposite ends of the binding groove

of the class I molecule, giving rise to a common orientation of the peptides in the binding site (Engelhard at page 14, column 1, lines 16-27, Curr. Opin. Biol. 1994, 6: 13-23, of record) Thus, the amino acid residues at the peptides' termini make a network of hydrogen bonds with conserved residues on the sides and bottom of the peptide binding groove of class I molecules. These interactions are important for holding the peptides in the binding groove and for stabilizing the complex (Guo *et al* at page 366, column 1 lines 1-10, Nature 1992, 360: 364-366, of record) "...the preferred length (of the peptide) is determined by the minimum amount of peptide required to span the center of the binding site and optimize the interactions at the ends", but that the predominant length is 9 amino acid residues (Engelhard at page 14, column 1, lines 23-27, of record).

The specification discloses that some nonamer and decamer peptides that are subsequences of human survivin or substitution variants of said peptides can bind to selected HLA class I molecules (especially Table 4). The specification discloses that five stage IV melanoma patients were vaccinated with the modified HLA-A2 restricted sur1M2 peptide (SEQ ID NO: 5) loaded onto autologous dendritic cells, resulting in a strong T cell response to said peptide, and the detection of infiltration of survivin reactive cells into visceral and soft tissue metastases using *in situ* peptide/HLA-A2 multimer staining (page 44 at lines 4-11). The specification discloses that SEQ ID NO; 1, 4 and 5 bind to HLA-A2 with *C50* of 30, 1 and 1 uM, respectively, and that CTL or TIL from some CLL or melanoma patients could recognize or cross-react with complexes of SEQ ID NO: 5 and HLA-A2 (especially Table 1). The specification discloses injection of dendritic cell loaded SEQ ID NO: 5, 10 or 3 into cancer patients, and demonstration of induction of HLA-A2/SEQ ID NO: 10-specific T cells with the capacity to home to soft tissue and visceral metastases (especially pages 44-48), but does not disclose the relevance of the treatment with the clinical outcome observed, *i.e.,* how the composition or vaccine comprising the peptides treat or prevent cancer.

Evidentiary reference Matthias *et al* (Blood. 2005, 106(11), part 2, pp 369B, abstract 3, 5145, of record) teach that a survivin peptide specific CTL could be detected in individuals with multiple myeloma, and those same CTL were detected in 5% of healthy individuals.

Evidentiary reference Celis (J. Clin. Invest. 2002, 110(12: 1765-1768, of record) teaches that "Unfortunately, the advantages that peptide vaccines have to offer are to some extent diminished by their inherent lack of immunogenicity, which so far has been reflected by their not-so-spectacular results in the clinic. Because the immune system in most species has evolved through time to fight life threatening infectious agents (and perhaps tumors), it should not be surprising that vaccines consisting of aseptic, endotoxin-free peptides are likely to be ignored and will likely be ineffective at inducing T cell immunity. In addition, peptides that are injected in aqueous solutions will be unsuccessful at stimulating

CTL responses, either because of their rapid biodegradation (*e.g.*, by proteases) or, worse, because of the induction of T cell tolerance/anergy, which results from the antigenic stimulation of CTLs by non-professional APCs." Celis further teaches that an additional complication resulting from the use of synthetic peptide-derived vaccines is the induction of low affinity CTLs, that while capable of killing target cells that are exogenously pulsed with peptide, are not able to recognize the target cells that naturally process and present the peptide epitope, such as malignant cells. These low quality CTLs would have little effect in fighting and controlling disease (especially page 1765 through the paragraph spanning pages 1765-1766.

Evidentiary reference Marchand *et al* (Exp. Opin. Biol. Therapy. 1(3): 497-510, 2001, of record) teach "It is fair to say that in patients vaccinated with defined antigen, the immune responses induced have been so far very poor, if present. In some studies, immune responses were reported for some patients but without any correlation with the clinical responses. In addition, some patients with complete and long-term regressions of several melanoma metastases failed to mount a detectable response against the antigen present in the vaccine." (last paragraph at column 2 on page 505).

Evidentiary reference Morel *et al* (Immunity 12: 107-117, 2000, of record) teach the treatment of target cells for at least one week with IFN-γ to induce immunoproteasome expression in said target cells, and further teach that a number of antigenic peptides that are efficiently produced by the standard proteasome are not produced by the immunoproteasome. Morel *et al* further teach that a major difference between the two forms of proteasomes in terms of catalytic activity is the severely reduced ability of the immunoproteasome to cleave after acidic residues and also after residues with branched side chains, such as valine (paragraph spanning pages 113-114). Morel *et al* teach that an IFN-γ rich environment such as that found in a lymph node or a tumor mass heavily infiltrated with T cells could cause a proteasome switch in the tumor cells resulting in a lack of presentation of certain tumor antigens and escape from CTL attack (especially first sentence of the third full paragraph at column 1 on page 114).

Evidentiary reference Andersen *et al* (Cancer Res. 2000, 61: 869-872, IDS reference) teach that they have demonstrated the existence of T cell responses against two survivin deduced epitopes in cancer patients, and "However, at this time we do not know whether *survivin* peptides are actually presented by the tumor cells *in vivo*, because the formal proof for this notion is still lacking" (last paragraph of article).

Evidentiary reference Andersen *et al* (Cancer Res. 2001, 61: 5964-5968, IDS reference) teach that "The ELISPOT methodology represents a strong tool to monitor peptide-specific T-cell response. However, although it has been shown that ELISPOT reactivity in most cases correlates with the capacity to lyse the target cell, the formal proof for this notion can be given only directly" (page 5966 at column 2, lines 3-7).

The specification discloses that SEQ ID NO: 36 recited in the pharmaceutical composition of instant claim 27 does bind HLA-A1 with a *C50* of 1 uM, but does not disclose if the peptide is immunogenic, and does not disclose that the second peptide in the said pharmaceutical composition SEQ ID NO: 14 binds any HLA class I molecule or is immunogenic (especially Table 4). The disclosed use of a pharmaceutical composition of the invention is to treat cancer ([0022]).

Evidentiary reference Andersen *et al* (Cancer Res. 2000, 61: 869-872, IDS reference) teach that the peptide STFKNWPFL (that is SEQ ID NO: 14 of instant claim 27) does not bind HLA-A2 (especially Table 1), thus indicating that the said peptide would not be useful in a pharmaceutical composition to treat and HLA-A2 positive patient.

Evidentiary reference Reker *et al* (Cancer Biol. & Therapy. 2004, 3(2): 173-179, of record) teach "To date, it is not known whether survivin is indeed a tumor rejection antigen, *i.e.,* a tumor-associated antigen that can elicit immune responses in patients, which significantly impacts tumor growth...Thus if efficient immunity can be successfully elicited in cancer patients, without the induction of severe autoimmunity, survivin clearly becomes a prime candidate for a widely applicable cancer vaccine" (last paragraph of article).

The specification does not disclose any peptide or composition thereof used prophylactically as a vaccine.

Evidentiary reference the Merck Manual (of record) teaches that a vaccine is a suspension of whole or fractionated bacteria or viruses that have been rendered nonpathogenic and is given to induce an immune response and prevent subsequent disease.

Evidentiary reference Encyclopedia Brittanica Online (of record) defines vaccine as a suspension of weakened, killed, or fragmented microorganisms or toxins or of antibodies or lymphocytes that is administered primarily to prevent disease.

The art recognizes that in order to be used for generating an immunogenic response, *i.e.,* for it to be an epitope, and also hence by extension to be used for *ex vivo* or *in situ* diagnosis of survivin reactive T cells of a cancer patient, that the said peptide must bind MHC and also present an epitope recognized by T cells.

There is no disclosure in the specification that the peptides consisting of or comprising SEQ ID NO: 1, 4, 14 and 36 constitute a T cell epitope.

Even if there were factual evidence that patients with melanoma or any other cancer or pathological condition could produce a peptide-specific immune response to the claimed peptide in a pharmaceutical composition, there is no factual evidence that the patient's condition would clinically improve, *i.e.,* be 'treated', nor that a vaccine comprising the peptide could prevent a cancer. Based upon the teachings of the evidentiary references cited herein, it is evident that eliciting an immune response is not sufficient to evoke a clinically significant or specific anti-tumor effect.

Therefore, because of the demonstrated unpredictability in the art of cancer immunotherapy and in the absence of sufficient exemplification and guidance, one skilled in the art cannot make and/or use the claimed invention with a reasonable expectation of success. Undue experimentation would be required of one skilled in the art to practice the instant invention. See *In re Wands* 8 USPQ2d 1400 (CAFC 1988).

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in the amendment filed 9/24/07 on pages 22-23, briefly that: (1) SEQ ID NO: 1, 4 and 5 bind to HLA-A2, with the latter two binding with almost similar high affinity to HLA-A2 as a positive control, (2) Examples 2 and 5 evaluated responses to survivin-derived peptide epitopes, for SEQ ID NO: 5, and the Office Action has acknowledged enablement for SEQ ID NO: 5, (3) in the declaration under 37 CFR 1.132 of Dr. Mads Hald Andersen, Dr. Andersen states his opinion "the clinical relevance of using the other peptide species in cancer therapy is supported by the fact that in relation to the subject surviving tumor associated antigens, it is not possible to identify a single dominant epitope peptide, and that in addition the inclusion of more peptide species may provide for the targeting of multiple HLA alleles/molecules", (4) with regard to the Reker *et al* reference, Dr. Andersen states the "statement was presented in the discussion of the research data, not to express concerns with respect to the relevance of using surviving peptides in cancer immunotherapy, but merely to indicate that phase III clinical trials-the only firm proof that a vaccine works-had not yet been completed."

It is the Examiner's position that: (1) the fact that SEQ ID NO: 1 and 4 bind to HLA-A2 is not indicative that they are T cell epitopes, or that they can be used to treat or prevent cancer, (2) Examples 2 and 5 do not disclose a clinical response for treatment or prevention using SEQ ID NO: 5, and Example 5 discloses that a T cell response could be elicited when dendritic cells were pulsed with SEQ ID NO: 5 and administered *in vivo* and T cell infiltration of metastases could be observed, and the instant rejection does not acknowledge enablement for SEQ

ID NO: 5 except for the peptide consisting of SEQ ID NO: 5, kit thereof, HLA-A2/complex or multimer complex thereof, not for the vaccine, pharmaceutical composition or other compositions as enunciated supra, (3) regardless of whether other peptide species might be used if they are T cell epitopes that are expressed on a tumor cell and can elicit an anti-tumor T cell response that results in a clinical outcome for treatment, the peptides and compositions thereof that are not enabled as discussed supra have not been disclosed to be expressed on a tumor cell or to elicit a T cell response or treat or prevent a cancer, and the instant claims are drawn to peptides that bind to HLA-A2 except for SEQ ID NO: 14 and that latter peptide has not been disclosed to produce a clinical outcome in treatment or prevention of a cancer, (4) Dr. Andersen confirms that the only firm proof that a peptide is a vaccine or pharmaceutical is administration in phase III clinical trials that have not been completed, and SEQ ID NO: 1, 4, 14 and 36 are not disclosed in said Reker *et al* reference.

6. Claim 24 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claim encompass a peptide that is capable of eliciting INF-gamma producing cells in a PBL population of a patient having a cancer disease, said INF-gamma producing cells having cytotoxic effect against survivin expressing cells of a cancer cell line, including a line selected from the group consisting of the breast cancer cell line MCF-7 and the melanoma cell line FM3. There is insufficient disclosure in the specification on such cell lines.

It is noted by the Examiner that Applicant's amendment filed 9/24/07 (on page 24) as well as the said declaration of Dr. Andersen under 37 CFR 1.132 (at item #6 on page 3) states "[t]he cell line was originally described by Kirkin *et al* (Cancer Immunol. Immunother, 41: 71-81, 1995) and is well recognized within the art." However, the cell line must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public as enunciated below.

The MF3 cell line is essential to the claimed invention. The reproduction of an identical cell line is an extremely unpredictable event. The cell line must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The instant specification does not disclose a repeatable process to obtain the cell line, and it is not apparent if the cell line is readily available to the public.

If a deposit was made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicants, assignees or a statement by an attorney of record over his or her signature and registration number stating that the deposit has been made under the provisions of the Budapest Treaty and that all

restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application is required.

If a deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. 1.801-1.809, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(A) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(B) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(C) the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample or for the enforceable life of the patent whichever is longer;

(D) a viability statement in accordance with the provisions of 37 C.F.R. 1.807;

(E) the deposit will be replaced should it become necessary due to inviability, contamination, or loss of capability to function in the manner described in the specification.

Furthermore, unless the deposit was made at or before the time of filing, a declaration filed under 37 C.F.R. 1.132 is necessary to construct a chain of custody. Cell line .... was deposited after the time of filing. The declaration, executed by a person in a position to know, should identify the deposited cell line by its depository accession number, establish that the deposited cell line is the same as that described in the specification, and establish that the deposited plasmid was in Applicants possession at the time of filing. *In re Lundak*, 27 USPQ 90.

Biological materials must be known and readily available to the public (See MPEP 2404.01). Neither concept alone is sufficient. The Office will accept commercial availability as evidence that a biological material is known and readily available only when the evidence is clear and convincing that the public has access to the material. A product could be commercially available but only at a price that effectively eliminates accessibility to those desiring to obtain a sample. The relationship between the applicant relying on a biological material and the commercial supplier is one factor that would be considered in determining whether the biological material was known and readily available. However, the mere fact that the biological material is commercially available only

through the patent holder or the patent holder's agents or assigns shall not, by itself, justify a finding that the necessary material is not readily available, absent reason to believe that access to the biological material would later be improperly restricted.

Therefore, because of the unpredictability in the art of making an identical cell line, and by extension a peptide that is capable of eliciting cells that have a cytotoxic effect against said cell lines, one skilled in the art cannot make and/or use the claimed invention with a reasonable expectation of success. Undue experimentation would be required of one skilled in the art to practice the instant invention. See *In re Wands* 8 USPQ2d 1400 (CAFC 1988).

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 20 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

a. Claim 20 is indefinite in the recitation of "A peptide ...comprising, for each specific HLA allele, any of the amino acid residues as indicated in the following table" because it is not clear what is meant, *i.e.,* only HLA-A2 is listed in the table.

b. Claim 24 is indefinite in the recitation of "the breast cancer cell line MCF-7 and the melanoma cell line FM3" because their characteristics are not known. The use of "MCF-7 and FM3" as the sole means of identifying the claimed cell lines renders the claim indefinite because "MCF-7 and FM3" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designations to define completely distinct cell lines.

Applicant's arguments to the rejection of claim 24 have been fully considered, but are not persuasive.

Applicant's said arguments appear on page 24 of the amendment filed 9/24/07.

It is the Examiner's position that although the breast cancer cell line MCF-7 is commercially available and has ATCC number HTB-22TM, such accession number is not recited in the claim. It is the Examiner's further position that just because a cell line such as FM3 was described in a publication, it is not an indication that said cell line is commercially available or that FM3 is the same cell line that is the FM3 cell line taught by the publication.

9. For the purpose of prior art rejections, the filing date of the instant claims 1, 17, 20-28, 32-40 and 50 is deemed to be the filing date of the instant application, *i.e.,* 11/19/03, as neither the parent application serial no. 10/354,090 nor the parent provisional application 60/352,284 support the claimed limitations of the instant application. It is noted by the Examiner, that although SEQ ID NO: 1, 4, 5 and 14 are disclosed in the said provisional parent application, and SEQ ID NO: 1, 4, 5, 14 and 36 are disclosed in the 10/354,090 parent application, the limitations of claim 1 are not disclosed in either, *i.e.,* "A MHC class I-restricted epitope peptide derived from survivin comprising an epitope peptide selected from SEQ ID NO: 1, 4, 5 and 14. In addition the parent provisional application does not disclose SEQ ID NO: 36.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1, 17, 20-24, 36 and 38-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Andersen *et al* (Cancer Res. 2/2001, 61: 869-872, IDS reference) as evidenced by Andersen *et al* (Cancer Res. 2001, 61: 5964-5968, IDS reference).

Andersen *et al* teach the human survivin peptides with the sequences STFKNWPFL (does not bind to HLA-A2.1), FLKLDRERA (30 uM), TLPPAWQPFL (30 uM), ELTLGEFLKL (10 uM), LLLGEFLKL (1 uM, substitution analog peptide), and LMLGEFLKL (1 uM, substitution analog peptide), that correspond to SEQ ID NO: 14, 1, 2, 3, 4 and 5 of the instant claims, respectively. Andersen *et al* further teach that these peptides have *C50* (uM) values as determined in an assembly assay for peptide binding to HLA-A2.1 molecules as indicated above. Andersen *et al* teach that a CLL cancer patient's IFN-γ producing PBL responded strongly against the analog peptide LMLGEFLKL at 35 per 10^4 cells in an ELISPOT assay (see entire reference, especially Table 1 and Results).

Evidentiary reference Andersen *et al* (2001) teach the human servivin peptides ELTLGEFLKL (SEQ ID NO: 3 of the instant claims) and the substitution analog peptide LMLGEFLKL (SEQ ID NO: 5 of the instant claims). Andersen *et al* teach that the LMLGEFLKL peptide could be used to isolate and stimulate CTL that

produce INF-γ, and that these CTL could lyse (*i.e.,* could exhibit cytotoxicity against the) HLA-A2 positive breast cancer cell line MCF-7 and the HLA-A2-positive melanoma cell line FM3 (see entire reference, especially results).

Claims 38-40 are included in this rejection because the art reference teaches complexes of the survivin HLA-A2-binding peptides with HLA-A2.1, and wherein the HLA/peptide complexes are contacting a T cell, they are multimeric. The instant claims do not recite wherein the complex is isolated.

Claim 36 is included in this rejection because the peptides were used in solution when added to the ELISPOT wells, *i.e.,* were in a composition that was used for *ex vivo* detection or diagnosis of the presence in a cancer patient of survivin reactive T cells among PBL. In addition, the intended use of the composition comprising the peptide "for *ex vivo* or *in situ* diagnosis" recited in the said claims does not carry patentable weight *per se*, and the claims read on the active or essential ingredients of the composition.

Applicant's arguments have been fully considered, but are not persuasive. Applicant's arguments are of record in the amendment filed 9/24/07 on pages 25-26, briefly that the art reference was published February 2001, rather than February 2000, the priority date for art is 1/30/02 based upon the filing date of parent provisional application 60/352,284, and the declaration under 37 CFR 1.132 of Dr. Andersen sets for the contribution of the non-inventor and inventor authors of the Andersen publications.

It is the Examiner's position that the instant claims do not have support in the parent provisional application 60/352,284 as enunciated supra, and although the publisher of the Andersen art reference notated an incorrect publication date, the art reference is still a 102(b) art reference that constitutes a statutory bar that can not be overcome by a Katz-type declaration.

12. Claims 1, 17, 20-24, 36 and 38-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Andersen *et al* (Cancer Res. 2001, 61: 5964-5968, IDS reference).

Andersen *et al* teach the human servivin peptides ELTLGEFLKL (SEQ ID NO: 3 of the instant claims) and the substitution analog peptide LMLGEFLKL (SEQ ID NO: 5 of the instant claims). Andersen *et al* teach that HLA-A2/peptide complexes were multimerized, that the LMLGEFLKL peptide could be used to isolate and stimulate CTL that produce INF-γ, and that these CTL could lyse (*i.e.,* exhibit cytotoxicity against) the HLA-A2 positive breast cancer cell line MCF-7 and the HLA-A2-positive melanoma cell line FM3. Andersen *et al* also teach the survivin LTLGEFLKL nonamer peptide (see entire reference, especially results).

Claim 36 is included in this rejection because the peptides were used in solution when added to the ELISPOT wells, *i.e.,* were in a composition that was used for *ex vivo* detection or diagnosis of the presence in a cancer patient of survivin reactive T cells among PBL. In addition, the intended use of the composition comprising the peptide "for *ex vivo* or *in situ* diagnosis" recited in the said claims does not carry patentable weight *per se*, and the claims read on the active or essential ingredients of the composition.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in the amendment filed 9/24/07 on page 26, briefly that the art reference was published February 2001, rather than February 2000, the priority date for art is 1/30/02 based upon the filing date of parent provisional application 60/352,284, and the declaration under 37 CFR 1.132 of Dr. Andersen sets for the contribution of the non-inventor and inventor authors of the Andersen publications.

It is the Examiner's position that the instant claims do not have support in the parent provisional application 60/352,284 as enunciated supra, and although the publisher of the Andersen art reference notated an incorrect publication date, the art reference is still a 102(b) art reference that constitutes a statutory bar that can not be overcome by a Katz-type declaration.

13. Claims 1, 17, 20-24, 36 and 38-40 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 6,346,389.

U.S. Patent No. 6,346,389 discloses a 37-mer peptide comprising the subsequence STFKNWPFL that corresponds to SEQ ID NO: 14 of the instant claims. the 37-mer peptide is SEQ ID NO: 15 of the art reference and the art reference discloses that said peptide is the amino acid sequence from the beginning of the coding region of the human survivin gene.

14. Claims 1, 17, 20-24, 36 and 38-40 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,346,389.

U.S. Patent No. 6,346,389 discloses a 37-mer peptide comprising the subsequence STFKNWPFL that corresponds to SEQ ID NO: 14 of the instant claims. the 37-mer peptide is SEQ ID NO: 15 of the art reference and the art reference discloses that said peptide is the amino acid sequence from the beginning of the coding region of the human survivin gene.

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 1, 17, 20-25, 28 and 32-37 are rejected under 35 U.S.C. 103(a) as being obvious over WO 00/03693 A1 (IDS reference) in view of Rammensee *et al* (MHC Ligands and Peptide Motifs. Springer, Landes Bioscience, USA, pages 217-228 and 238-243, 1997, of record), Ruppert *et al* (Behring Inst. Mitt., No. 94, 48-60 (1994), Conway *et al* (Blood, 2/15/00, 95(4): 1435-1442) and U.S. Patent No. 6,572,864 (of record).

WO 00/03693 A1 teaches vaccines that comprise an antigen that comprises one or more epitopes of survivin protein, including Class I MHC epitopes, or that comprises peptide fragments that bind to MHC class I, said vaccine in a pharmaceutically acceptable carrier, said vaccine for eliciting an antitumor immune response, including CTL response to Class I MHC epitopes, wherein the cancer patient has cancer of the colon, lung, bladder, stomach, breast, cervix, or lymphoma or leukemia, and wherein the cancer patient is human, *i.e.,* the patient has HLA class I molecules (see entire document, especially abstract, page 4 at the first four paragraphs, page 5 at the first two full paragraphs, page 6 at lines 9-21, page 11 at lines 15-30, claims, page 9 at the first two paragraphs, page 13 at lines 4-21, page 14 at lines 10-18).

WO 00/03693 A1 does not teach wherein the peptide is one of the sequences recited in base claim 1, nor one restricted by HLA-A2, nor wherein said peptide is a nonamer peptide, nor wherein the peptide comprises any of the amino acid residues recited in instant claim 20, nor wherein the peptide is capable of eliciting INF-γ producing cells in a PBL population of a cancer patient at the frequency recited in instant claim 21, nor a pharmaceutical composition or kit thereof. WO 00/03693 A1 (IDS reference) does not teach wherein the peptide is present in a kit (claim 37).

Rammensee *et al* teach predictive methods for selecting candidate HLA-A2 binding peptides, *i.e.,* motifs for peptides that bind to HLA-A2 and a length of 8-11 amino acid residues, and for epitope prediction. Rammensee *et al* teach that the canonical motif amino acid residues for HLA-A2 binding peptides are: L or M at position 2 of the peptide and V or L at the carboxy terminal position of the peptide (see pages 217-228 and 237-243).

Ruppert *et al* teach that factors other than canonical main anchor residues significantly contribute to the binding characteristics of a given peptide (second full paragraph at column 1 on page 52). Ruppert *et al* teach an extended motif for peptides that bind to HLA-A2 is L, M, I, V, A or T at position 2 (P2) and L, V, I, A, M or T at position 9 or 10 (P9 or P10) (especially Table 3). Ruppert *et al* further teach that HLA-A2.1 is expressed by a large proportion of individuals of different ethnic backgrounds (especially paragraph spanning pages 50-51). Conway *et al* teach the sequence of human surviving protein (especially Figure 2).

U.S. Patent No. 6,572,864 (of record) discloses formulating peptide epitopes in a suitable diluent such as saline or water or adjuvants, and preparing the peptides or analogs thereof in a kit, alone or in combinations with other reagents for use in immunoassay or for use in a pharmaceutical composition (especially column 12 at lines 6-25, and column 21 at lines 44-65).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have scanned the sequence of *survivin* protein taught by WO 00/03693 A1 and by Conway *et al* for subsequences that bind to the MHC class I molecule HLA-A2 taught by Rammensee *et al* using the predictive methods taught by Rammensee *et al,* using the extended motif taught by Ruppert *et al*, in order to produce the nonamer peptide sequence FLKLDRERA (SEQ ID NO: 1) and the nonamer subsequence STFKNWPFL (SEQ ID NO: 14) and to have made synthetic peptide versions of these subsequences and to have combined them with saline or another pharmaceutically acceptable diluent as disclosed by U.S. Patent No. 6,572,864 and including in combination with other epitopes such as in the multiepitope composition taught by WO 00/03693 A1 for eliciting an antitumor T cell response against the class I restricted epitopes.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to select candidate peptides for HLA-A2 as per the teaching of Rammensee *et al* to test for potential use in the compositions taught by WO 00/03693 A1, including in pharmaceutical compositions disclosed by U.S. Patent No. 6,572,864. One of ordinary skill in the art at the time the invention was made would have been motivated to use the extended motif taught by Ruppert *et al* due to the lack of nonamer peptide subsequences in the human survivin protein sequence taught by Conway *et al* that possess canonical anchor residues at both P2 and P9.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have put the peptide(s) taught WO 00/03693 A1 in a kit form as disclosed by U.S. Patent No. 6,572,864.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this for convenience of use because U.S. Patent No. 6,572,864 discloses putting peptide immunogens in a kit.

Claim 17 is included in this rejection because the peptide fragment epitope(s) is/are derived from human survivin protein by deleting at least one amino acid residue from the intact protein.

Claim 36 is included in this rejection because the peptides were used in a composition; the intended use of the composition comprising the peptide "for *ex vivo* or *in situ* diagnosis" recited in the said claims does not carry patentable weight *per se*, and the claims read on the active or essential ingredients of the composition.

With regard to the claims that recite "vaccine," if the vaccine merely comprises a known composition, the term carries little weight absent evidence of structural difference.

With regard to the inclusion of claims 21, 22 and 24 in this rejection, the claimed peptide appears to be similar to the peptide composition of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the peptide composition of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

17. Claims 38-40 are rejected under 35 U.S.C. 103(a) as being obvious over WO 00/03693 A1 (IDS reference) in view of Rammensee *et al* (MHC Ligands and Peptide Motifs. Springer, Landes Bioscience, USA, pages 217-228 and 238-243, 1997, of record), Ruppert *et al* (Behring Inst. Mitt., No. 94, 48-60 (1994), Conway *et al* (Blood, 2/15/00, 95(4): 1435-1442) and U.S. Patent No. 6,572,864 as applied to claims 1, 17, 20-25, 28 and 32-37 above, and further in view of WO 99/50637.

The combination of WO 00/03693 A1, Rammensee *et al*, Ruppert *et al*, Conway *et al* and U.S. Patent No. 6,572,864 has been discussed above, hereafter referred to as "the combined references."

The combined references do not teach a complex comprising the peptide of claim 1 and a class I HLA molecule or a fragment of such a molecule.

WO 99/50637 A2 teaches immune complexes that are tetramers that comprise an MHC molecule such as HLA-A2.1, an antigenic peptide, β2m, streptavidin as the binding molecule, and further comprising a label such as a fluorescent, enzymatic or radioactive label, and that the complexes are useful for monitoring

T cell responses or for isolating T cells (especially abstract, page 8 at lines 10-22, page 11 at line 21, page 62 at lines 1-14, page 63 at lines 1-4, claims).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made tetrameric complexes such as taught by WO 99/50637 A2 using the HLA-A2.1 molecule taught by WO 99/50637 A2 and a peptide taught by the combined references.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to monitor T cell responses or to isolate T cells as taught by WO 99/50637 A2, especially in light of the teachings of the combined references that teaches making nonameric subsequences of the Survivin protein that have the HLA-A2.1 binding motif and using the peptides to elicit a T cell response.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a monomer first by linking the peptide to the HLA molecule genetically, expressing the monomer, and then constructing the tetramer.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order that the HLA molecules be preloaded with peptide.

18. The declaration of Dr. Andersen under 37 CFR 1.132 has overcome the prior 103(a) rejections of record based upon the two Andersen et al references, *i.e.,* Cancer Research 61, 869-72, 2001 and Cancer Research 61, 5964-5968, 2001.

19. No claim is allowed.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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December 4, 2007

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